Circular Dichroism of a Carbocation. (1*S*,2*R*)-Dimethyl(2-methylcyclopropyl)carbenium Ion

Robert G. Ghirardelli[1]

Contribution from the Stauffer Laboratories of Stanford University, Stanford, California 94305. *Received February 22, 1973*

Abstract: (*S*)-2-Methyloxirane was prepared from ethyl (*S*)-lactate in a convenient five-step procedure and then converted by reaction with triethyl phosphonoacetate anion into (1*R*,2*R*)-2-methylcyclopropanecarboxylic acid. The derived acyl chloride reacted with 2 equiv of methylmagnesium iodide to give (1*R*,2*R*)-α,α,2-trimethylcyclopropanemethanol. This tertiary alcohol was introduced into 90% fluorosulfonic acid–10% antimony pentafluoride at low temperature to give a solution of (1*S*,2*R*)-dimethyl(2-methylcyclopropyl)carbenium ion whose circular dichroism spectrum showed a negative Cotton effect at 295 nm. The degree of ellipticity was distinctly temperature dependent.

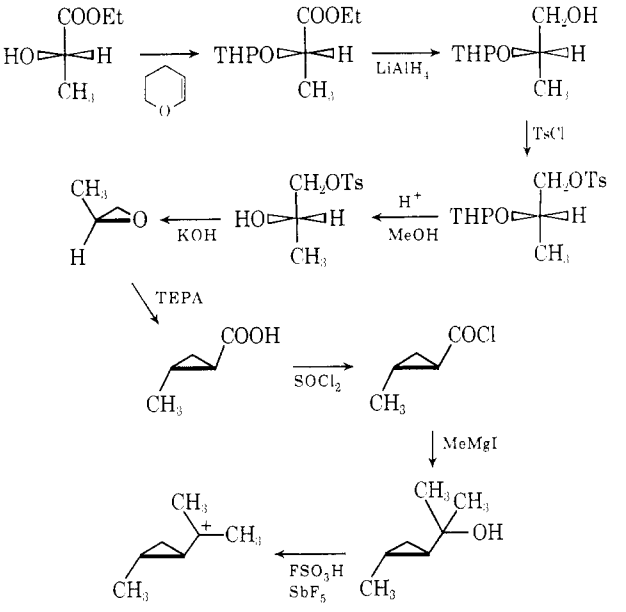
Over the past several years a considerable number of carbocations have been prepared in strongly acidic media, and preserved long enough at low temperatures to allow characterization by their spectral and chemical properties. The research groups of Deno, Richey, and especially Olah have pioneered in this area, and a sizable body of information[2] now exists in which the properties of these ions correlate with their structures in a satisfying manner. The techniques employed in these studies have included nuclear magnetic resonance, and to a lesser extent ultraviolet absorption spectroscopy. It was intriguing to consider whether a dissymmetric carbocation could be generated in such media, so as to allow its circular dichroism[3] (CD) to be determined, since the CD spectrum has the potential to provide the chemist with information about the configuration of his subject, and thus perhaps its history[4] as well. The present investigation was begun in order to test the feasibility of the method.

It is of course a necessary condition that the substrate for any CD study be dissymmetric, and desirable that it possess an absorption band in an accessible region of the electronic spectrum. Fulfillment of both conditions manifests itself in the display of a Cotton effect. The choice of a suitable carbenium[5] ion narrowed to a substituted dimethylcyclopropylcarbinyl ion for several reasons: the demonstrated relative stability (of the achiral parent ion) at −78° and knowledge that it exists with bisected geometry;[6] its possession of an intense uv absorption band;[7] the fact that much is known of the CD of the analogous cyclopropylcarbonyl compounds;[8] and the relationship to the *i*-cholesteryl system, and to the well-known conversions to and from cyclobutyl and allylcarbinyl cations.[9]

Results

Ethyl (*S*)-lactate was converted into its tetrahydropyranyl ether and the latter reduced to the corresponding ether of propylene glycol with lithium aluminum hydride, using procedures developed in these laboratories by others. Formation of the *p*-toluenesulfonate ester, followed by removal of the protecting tetrahydropyranyl group, gave an oil which on treatment with potassium hydroxide afforded a 44% overall yield of (*S*)-2-methyloxirane with a specific rotation of −7.77°. This sequence of steps is outlined in the first part of Scheme I, and is superior to previously published

Scheme I



methods[10] in that the optical purity of the oxide is over 90% of the highest value recorded, the overall yield (based on the relatively inexpensive ethyl lactate) is reasonable, and neither a lengthy fermentation step

(1) U. S. Army Research Office, Durham, N. C. 27706.

(2) For reviews, see (a) G. A. Olah, *Science*, **168**, 1298 (1970); (b) "Carbonium Ions," Vol. I–III, G. A. Olah and P. v. R. Schleyer, Ed., Wiley-Interscience, New York, N. Y., 1968–1972.

(3) For reviews of the use of circular dichroism in organic chemistry, see P. Crabbé, "ORD and CD in Chemistry and Biochemistry," Academic Press, New York, N. Y., 1972; "Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry," G. Snatzke, Ed., Heyden and Son, London, 1967; C. Djerassi, *Proc. Chem. Soc. London*, 314 (1964).

(4) G. A. Olah, C. L. Jeuell, D. P. Kelly, and R. D. Porter, *J. Amer. Chem. Soc.*, **94**, 146 (1972), especially footnote 18.

(5) The nomenclature of G. A. Olah [*J. Amer. Chem. Soc.*, **94**, 808 (1972)] has been adopted in this paper.

(6) C. U. Pittman, Jr., and G. A. Olah, *J. Amer. Chem. Soc.*, **87**, 5123 (1965).

(7) G. A. Olah, C. U. Pittman, Jr., R. Waack, and M. Doran, *J. Amer. Chem. Soc.*, **88**, 1488 (1966).

(8) C. Djerassi, W. Klyne, T. Norin, G. Ohloff, and E. Klein, *Tetrahedron*, **21**, 163 (1965).

(9) N. L. Wendler in "Molecular Rearrangements," P. de Mayo, Ed., Wiley-Interscience, New York, N. Y., 1964, p 1075; Vol. III of ref 2b, especially chapters by K. B. Wiberg and H. G. Richey.

(10) Critically reviewed by B. Franzus and J. H. Surridge, *J. Org. Chem.*, **31**, 4286 (1966).

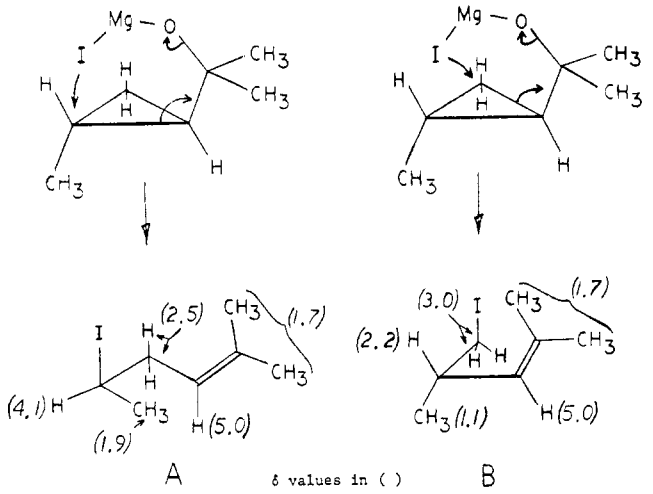


Figure 1.

nor chromatographic purification of any intermediate is necessary.

Treatment of the (*S*)-2-methyloxirane with the anion of triethyl phosphonoacetate (TEPA), following the procedure employed with the racemic compound by Deno,[11] gave on distillation a mixture of *cis*- and *trans*-2-methylcyclopropanecarboxylic acids with a calculated "specific" rotation of −69.7°. The reported[12] figure for the pure 1*R*,2*R* (trans) isomer is −77.4°, that for the 1*S*,2*R* (cis) is +28.6°. Clearly, the former is the major product, reflecting a stereochemical history involving inversion of configuration at the number two carbon. This result is consistent with the report of experiments with styrene oxide, as well as with Denney's[13] mechanism for the process.

Conversion to the acid chloride with thionyl chloride was (judging from the narrow distilling range) accompanied by enrichment of the mixture in the trans isomer, as has been found[14] in similar instances. A small sample was weighed and reconverted into the acid and showed a negative rotation at 589 nm with a specific magnitude calculated to be approximately 88°. Reaction of the acid chloride with 2 equiv of methylmagnesium iodide yielded the tertiary alcohol, and a by-product which mass spectral analysis showed to have the formula $C_7H_{13}I$. Its chemical properties suggested unsaturation; the proton nmr spectrum, while complex, could be resolved into individual signals and was compatible with an approximately 60:40 mixture of the two allylcarbinyl iodides resulting from cyclopropane ring opening by iodide ion (Table I). An analogous reaction has been reported[15] and possible mechanisms were discussed[16] by Sarel. The apparent slight discrimination between primary and secondary carbon attack could be evidence for the cyclic mechanism proposed earlier[16] and illustrated for the present case in Figure 1. The configuration of A is shown as

(11) N. C. Deno, W. E. Billups, D. La Vietes, P. C. Scholl, and S. Schneider, *J. Amer. Chem. Soc.*, **92**, 3700 (1970).
(12) R. G. Bergman, *J. Amer. Chem. Soc.*, **91**, 7405 (1969).
(13) D. B. Denney, J. J. Vill, and M. J. Boskin, *J. Amer. Chem. Soc.*, **84**, 3944 (1962).
(14) D. E. Applequist and A. H. Peterson, *J. Amer. Chem. Soc.*, **82**, 2372 (1960).
(15) J. Yovell, M. Sarel-Imber, and S. Sarel, *Isr. J. Chem.*, **4**, 21 (1966).
(16) S. Sarel, J. Yovell, and M. Sarel-Imber, *Angew. Chem., Int. Ed. Engl.*, **7**, 577 (1968).

Table I

δ (from Figure 1)		Relative integral values Calcd for 60A:40B	Found
C=CH	5.0	7.5	8
C_2ClH	4.1	4.5	5
$CClH_2$	3.0	6	6
C_2CH_2	2.5	9	10
C_3CH	2.2	3	3
$ClCH_3$	1.9	13.5	13
$C{=}C(CH_3)_2$	1.7	45	45
C_2CHCH_3	1.1	9	10

that resulting from top-side attack by iodide; attack opposite to the ring bond broken would lead to the enantiomer.

The tertiary alcohol was converted into the carbenium ion in "magic acid" using the ethanol dilution technique,[7] and was transferred rapidly after thorough stirring to a jacketed silica cell kept cold by a stream of refrigerated gaseous nitrogen.

Since the ethylhydronium ion gives interfering signals, a sample for pmr examination was prepared by freezing a drop of precursor alcohol on the walls of a test tube and rinsing it with the cold acid mixture. This inferior technique, coupled with the need to run the sample at −45° to attain reasonable resolution, resulted in some deterioration of the sample, manifested primarily in broad, complex resonance between δ 1.0 and 1.8, similar to what has been reported in related cases.[17] The most prominent signals were a doublet at δ 2.0 (relative to TMS) ascribed to the ring methyl, singlets at δ 2.7 and 3.15, and a complex at δ 3.7–4.0; these last are close to the shift values assigned to the carbinyl methyls and ring protons, respectively, of the dimethylcyclopropylcarbenium ion itself.[4]

Discussion

As seen in Figure 2, the circular dichroism spectrum of the (1*S*,2*R*)-dimethyl(2-methylcyclopropyl)carbenium ion in 90% fluorosulfonic acid–10% antimony pentafluoride (by weight) displays a negative Cotton effect at 295 nm. Only the relative values of the ellipticity should be considered, since their calculation is based on the assumptions that the tertiary alcohol was completely converted to ion, and that no change in volume occurred on cooling. The considerable temperature dependence is real and apparently not due to sample deterioration: the curves of Figure 2 were measured in the sequence B (−66°), C (−78°), A (−47°). This phenomenon is not new, but has been observed and discussed earlier;[18] among the explanations considered were conformational changes, solvation, and libration of the perturbing substituent. The dependence is more pronounced in the present experiment, perhaps because the substituents are more intimately coupled to the chromophore. Further study is in order to establish the reproducibility of the phenomenon, and if so its cause. The ultraviolet absorption spectrum showed a strong band centered at 290 nm, compared to the 289-nm band displayed by the dimethylcyclopropylcarbenium ion.[7]

(17) N. C. Deno, J. S. Liu, J. O. Turner, D. N. Lincoln, and R. E. Fruit, Jr., *J. Amer. Chem. Soc.*, **87**, 3000 (1965).
(18) K. M. Wellman, W. S. Briggs, and C. Djerassi, *J. Amer. Chem. Soc.*, **87**, 73 (1965).

The shoulder in the region of the CD spectrum near 325 nm may arise either from degradation of a portion of the cyclopropylcarbinyl cation, or from a contaminant in the precursor alcohol. (Gas chromatographic analysis showed the presence of less than 2% of some material with slightly longer retention time.) The absorption of allyl cations generally occurs at lower wavelengths,[19] and although small displacements between uv and CD bands are common, it is difficult to visualize a reasonable path for the generation of such a cation in which chirality is preserved. The isomeric cyclopropylcarbenium ion with cis stereochemistry is another remote possibility to account for the 325-nm shoulder. There is no doubt, however, that the present work constitutes the first experimental demonstration of a Cotton effect for a carbenium ion.

Experimental Section

Ethyl L-lactate was obtained from Fluka (Buchs, Switzerland) as L(+)-milchsaure-aethylester. Infrared spectra were determined on a Perkin-Elmer Model 700 instrument, rotations on a Perkin-Elmer Model 141 polarimeter, pmr spectra on a Varian T-60, and circular dichroism spectra on a JASCO Model 5 spectropolarimeter.

Ethyl (*S*)-2-(Tetrahydro-2-pyranoxy)propanoate.[20] To a 500-ml, round-bottom flask containing 114 ml (118 g, 1 mol) of ethyl L-lactate was added first 152 ml (140 g, 1.67 mol) of dihydropyran and then 10 drops of 12 *N* HCl. A water bath was used to moderate the heat developed, and the solution was stirred magnetically for 16 hr. Na_2CO_3 (10 g) was added and stirring continued for 2 more hr. The material was filtered, concentrated on a rotary evaporator (50°), and then distilled through a short Vigreux column at reduced pressure to give 154 g (76%) of product with bp 66–68° (0.25 mm). More careful fractionation resulted in an extended boiling range, with evidence of a major and minor fraction. Two diastereomeric products are possible because the hetero ring introduces a second asymmetric carbon: ir (neat film) peaks near 2900, 1730, 1430, 1360, 1250, 1180, 1130–1080, 1020–1000, 970, 890, 860, 800 cm^{-1}; nmr (CCl_4) δ 1.2–1.8 (m, 12), 3.2–4.0 (m, 2), 4.2 (q, 3), 4.7 (broad s, 1).

(*S*)-2-(Tetrahydro-2-pyranoxy)-1-propanol.[21] To a cold (0°) solution of 12.0 g (0.32 mol) of $LiAlH_4$ in 400 ml of dry Et_2O, blanketed in N_2, was added over 2 hr a solution of 100 g (0.50 mol) of ethyl (*S*)-2-(tetrahydro-2-pyranoxy)propanoate in 150 ml of dry Et_2O. The ice bath was removed and the reaction mixture then refluxed gently for 48 hr. To the cooled mixture were added successively: 12 ml of H_2O; 9 ml of 20% NaOH solution; 20 ml of H_2O. There resulted on standing overnight (or longer) a white granular precipitate which was readily filtered (gravity). The filtrate was concentrated at atmospheric pressure and then distilled through a short Vigreux column at reduced pressure to give a major fraction with bp 64–66° (1 mm) and additional material boiling to 71°. The infrared spectra of the two mixtures were essentially identical, and showed a broad peak centered near 3450 cm^{-1}, strong absorption near 2900, 1130, 1020–1080, and 990 cm^{-1}, and sharp spikes near 1200, 940, 900, 870, and 810 cm^{-1} (as neat films).

(*S*)-1-(*p*-Toluenesulfonoxy)-2-(tetrahydro-2-pyranoxy)propane. To a cold solution of 40.0 g (0.25 mol) of 2-(tetrahydro-2-pyranoxy)-1-propanol in 75 ml of dry pyridine was added in small portions over 15 min 49.3 g (0.26 mol) of *p*-toluenesulfonyl chloride. Stirring was continued throughout the addition and overnight while the reaction mixture came to room temperature. The precipitated pyridine hydrochloride was filtered off and rinsed with 100 ml of C_6H_6 in three portions, and the combined filtrate and washings were concentrated on a rotary evaporator (60° bath). A 160-ml slurry of ice and water was added and the layers were separated. The aqueous phase was acidified slowly with 3 *N* HCl and extracted with two 40-ml portions of C_6H_6. The combined organic fractions were washed with 250 ml of cold 3 *N* HCl in three portions and twice with water and then dried over $MgSO_4$. The drying agent was filtered off and the filtrate concentrated on a rotary evaporator (65° bath) to give 80.5 g of clear oil with a residual odor of pyridine. The infrared spectrum (neat film) showed strong absorption at 2950, 1600, 1450, 1360, over the region 800–1200, and 660 cm^{-1}.

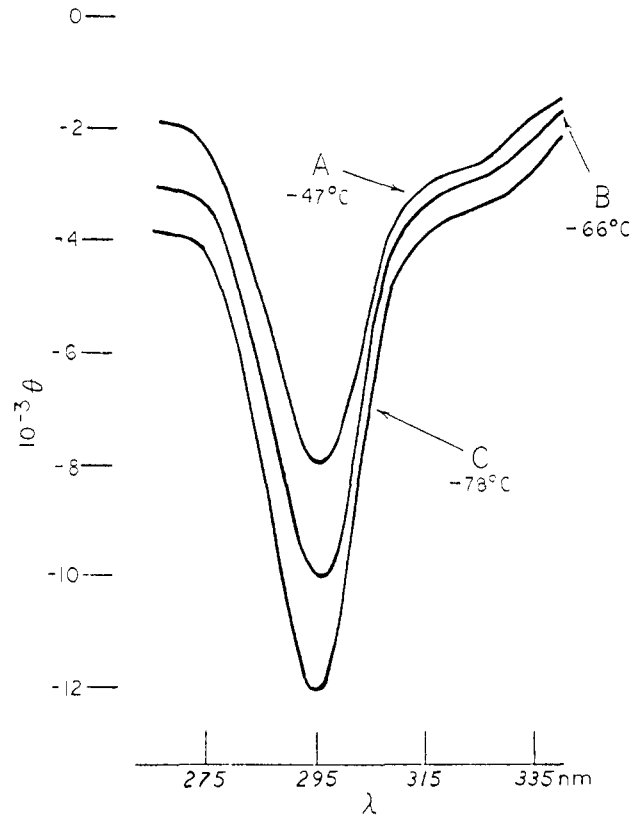


Figure 2. Circular dichroism spectra of (1*S*,2*R*)-dimethyl(2-methylcyclopropyl)carbenium ion.

(*S*)-1-(*p*-Toluenesulfonoxy)-2-propanol. The oil (80.5 g) from the above experiment was dissolved in 250 ml of dry MeOH, and 3 ml of 12 *N* HCl was added. After standing 36 hr the solution was brought to neutral pH with saturated $NaHCO_3$ solution (*ca.* 30 ml). Concentration on a rotary evaporator (65°) gave 62.0 g of an oil containing suspended salts. This could be used directly in the following step. A filtered sample (neat film) showed a broad OH peak centered at 3450 cm^{-1} and strong absorption at 3000, 1600, 1460, 1360, 1190, 1110, 990, 940, 830, and 680 cm^{-1}.

(*S*)-2-Methyloxirane. A 500-ml, round-bottom flask containing 0.25 mol (62 g including suspended salts) of (*S*)-1-(*p*-toluenesulfonoxy)-2-propanol was attached to a Claisen head and condenser leading to a receiver in an ice bath. First 100 g of KOH and then 35 ml of H_2O were added through the neck, which was immediately capped. Vigorous evolution of the oxide began after 2 min, and distillation continued at 35–37°. When it ceased, an additional 35 ml of H_2O was added, heat was applied, and collection was continued until the distillation temperature reached 95°. The 12 g of wet product was redistilled over KOH pellets and through a short Vigreux column to give 9.3 g (63%) of oxide boiling at 34.0–35.0°, $[\alpha]^{20}D$ −7.77° (*c* 0.032, $CHCl_3$).

2-Methylcyclopropanecarboxylic Acids. A solution of 28 g (0.125 mol) of triethyl phosphonoacetate in 15 ml of dry diglyme was added to 6.4 g (equivalent to 0.145 mol) of NaH (54.7% dispersion in oil) in the same solvent, all under N_2. Foaming necessitated frequent interruptions; after it ceased, 8.7 g (0.15 mol) of (*S*)-2-methyloxirane in 10 ml of dry diglyme was added over 15 min. The reaction mixture was stirred at room temperature for 45 hr, heated to 140° for 4 hr, and then cooled in an ice bath. Rapid addition of 18 g of NaOH in 30 ml of H_2O was followed by 16 hr reflux. The cooled mixture was added to 120 ml of water in a separatory funnel and washed three times with 60-ml portions of Et_2O. Sufficient 25% H_2SO_4 was added to bring the pH to 1.5, and extraction with 250 ml of Et_2O in six portions followed. The combined ether extracts were dried over $MgSO_4$ and then concentrated at atmospheric pressure and distilled through a 12-in. Vigreux column until about 20 ml of a yellow liquid remained.

(19) N. C. Deno, J. Bollinger, N. Friedman, K. Hafer, J. D. Hodge, and J. J. Houser, *J. Amer. Chem. Soc.*, **85**, 2998 (1963).

(20) Adapted from B. Winter, Ph.D. Thesis, Stanford University, 1970.

(21) Adapted from K. Sysak, Ph.D. Thesis, Stanford University, 1971.

This was distilled at 15 mm pressure through the same column to give, after a forerun (diglyme), 5.8 g of product boiling at 90–100° (most at 98–100°), $[\alpha]^{20}D$ −69.7° (*c* 0.025, $CHCl_3$).

(1*R*,2*R*)-2-Methylcyclopropylcarbonyl Chloride. A solution of 5.8 g (0.058 mol) of the above acid and 6 ml (9.7 g, 0.080 mol) of $SOCl_2$ in 19 ml of C_6H_6 was refluxed for 6 hr, and then the more volatile components were distilled through a 12-in. Vigreux column until the pot temperature reached 100°. Continuation at 70 mm pressure gave, after a forerun, 5.5 g (80%) of product boiling at 66.0–67.0°. A sample was treated with MeOH to give the methyl ester: bp 71.0° (90 mm); $[\alpha]^{20}D$ −90.3° (*c* 0.0301, MeOH); θ_{max} (227.5 nm) +114° (methanol). Another small sample was hydrolyzed to the acid and extracted with chloroform; assuming complete conversion and recovery, $[\alpha]^{20}D$ −88° (lit.[12] −77.4°).

(1*R*,2*R*)-α,α,2-Trimethylcyclopropanemethanol. To the Grignard formed from 2.4 g (0.100 mol) of Mg and 15.7 g (0.110 mol) of MeI in 65 ml of Et_2O, over N_2, was added with stirring 5.4 g (0.045 mol) of (1*R*,2*R*)-2-methylcyclopropylcarbonyl chloride in 30 ml of Et_2O. Stirring was continued at room temperature for 20 hr and then gentle refluxing for another 6 hr. Saturated NH_4Cl solution (75 ml) was added; the layers were separated and the organic solution was dried over $MgSO_4$. The ether was removed by distillation through a Vigreux column, and then the pressure was reduced to give 1.9 g (37%) of product: bp 79–81° (100 mm); $[\alpha]^{21}D$ −33.5° (*c* 0.0254, MeOH); nmr (CCl_4) δ 1.3 (s, 1), 1.15 (s, 6), 1.1–0.4 (complex 6–7); mass spectrum base peak at *m/e* 72, strong peaks at 59, 70, 81, 96, 99, weak parent peak; ir (neat film) strong OH, CH, other peaks at 1470, 1380, 1240, 1160, 1080, 1040, 960, 940, 910, 890, 860, 810 cm^{-1}. A higher boiling fraction (119–120° (100 mm) could be redistilled 72–74° (17 mm)) developed a violet color on standing in air and reacted with bromine: ir (neat film) 2900–3000, 1450, 1380, 1290 (weak), 1250 (weak), 1200, 1150, 1080, 840 cm^{-1}; mass spectrum base peak *m/e* 55, weak parent ion 224, strong peaks at 97, 83, 81, 69, 67, 53; nmr see Table I.

(1*S*,2*R*)-Dimethyl(2-methylcyclopropyl)carbenium Ion. Following the published procedure,[7] 26 mg (0.23 mmol) of (1*R*,2*R*)-α,α,2-trimethylcyclopropanemethanol was dissolved in 0.5 ml of 95% ethanol and added dropwise to 12 ml of 90% FSO_3H–10% SbF_5 (by weight) at −78° with vigorous stirring. After the mixture was stirred for an additional 10 min, a small sample was transferred *via* a prechilled syringe into a jacketed silica cell (0.2-mm path length) cooled with nitrogen. To minimize fogging, the cell was mounted in a plastic box with silica windows and the chamber of the spectropolarimeter purged continuously with dry nitrogen. Temperature was monitored by means of an iron–constantan thermocouple taped to the cell between the fill-ports.

Acknowledgment. These studies were carried out while the author was associated with the research group of Professor Carl Djerassi, whose encouragement and advice is deeply appreciated. He would also like to thank Edward Bunnenberg and Günter Barth for helpful advice, Ruth Records for obtaining the CD spectra, and Thomas Gibson for drawing his attention to ref 20 and 21. Thanks are also due Kenneth B. Wiberg and Herman Richey for graciously transmitting copies of their chapters in Vol. III of ref 2b prior to publication.

Carbon-13 Nuclear Magnetic Resonance Spectroscopy of Naturally Occurring Substances. XIX. *Aspidosperma* Alkaloids[1]

Ernest Wenkert,*[2a] David W. Cochran,[2a,3a] Edward W. Hagaman,[2a] F. M. Schell,[2a,3b] Norbert Neuss,[2b] A. S. Katner,[2b] Pierre Potier,[2c] Christiane Kan,[2c] Michel Plat,[2d] Michel Koch,[2d] Hachem Mehri,[2d] Jacques Poisson,[2e] Nicole Kunesch,[2e] and Y. Rolland[2e]

Contribution from the Department of Chemistry, Indiana University, Bloomington, Indiana 47401, Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana 46206, Institut de Chimie des Substances Naturelles, C.N.R.S., 91190 Gif-sur-Yvette, France, U.E.R. de Chimie Therapeutique de l'Université Paris-Sud, Paris 6e, France, and Faculté des Sciences Pharmaceutiques et Biologiques, Université Paris-Sud, Paris 6e, France. *Received February 12, 1973*

Abstract: The natural abundance ^{13}C nmr spectra of the *Aspidosperma* alkaloids tabersonine and vincadifformine, of the structurally related, new bases vandrikidine, vandrikine, and hazuntinine, of the indole–indoline alkaloid vincaleukoblastine (VLB) and leurosine, and of the indoline alkaloid vindoline and suitable models have been recorded. Chemical shift assignments have been made for all carbons of the alkaloids except some of the carbomethoxyvelbanamine portions of the indole–indoline alkaloids. The data have been used for the structure determination of the new indole bases and for ascertaining the presence of an epoxide linkage in leurosine. Anomalous, hence potentially misleading single frequency off-resonance data are described. A structurally diagnostic, endocyclic homoallyl shielding effect is portrayed by the use of a variety of models.

Upon completion of the ^{13}C nmr spectral analysis of the yohimboid and ajmalicinoid indole alkaloids,[4] a similar study of the structurally more complex *Aspidosperma* alkaloids was undertaken. The investigation was initiated by an inspection of the spectra of tabersonine (**1**) and vincadifformine (**2**), two compounds whose structures are representative of the basic ring skeleton of a large number of these natural substances.

The natural abundance ^{13}C nmr spectra of 0.2–1.0 *M* chloroform or deuteriochloroform solutions of the above compounds and others (*vide infra*) were recorded on a Fourier transform spectrometer operating at

(1) For the preceding paper, see E. Wenkert, J. S. Bindra, C.-J. Chang, D. W. Cochran, and F. M. Schell, manuscript submitted for publication.

(2) (a) Indiana University; (b) Eli Lilly and Company; (c) Institut de Chimie des Substances Naturelles; (d) U. E. R. de Chimie Thérapeutique; (e) Faculté des Sciences Pharmaceutiques et Biologiques.

(3) (a) U. S. Public Health Service predoctoral fellowship recipient, 1967–1971; (b) U. S. Public Health Service predoctoral fellowship recipient, 1969–1972.

(4) D. W. Cochran, Ph.D. Dissertation, Indiana University, 1971.